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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/776,350	04/18/97	MACLEAN	A 117-231

HM22/0301

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EXAMINER	
UNGAR,S	
ART UNIT	**PAPER NUMBER**
1642	21

DATE MAILED: 03/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/776,350	MacLean et al
Examiner	**Group Art Unit**
Ungar	1642

☒ Responsive to communication(s) filed on *Dec 30, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *43-58* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *43-58* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The request filed on December 30, 1999 (Paper No. 18) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/776,380 is acceptable and a CPA has been established. An action on the CPA follows.

2 The Claims 20, 22-30 and 32-42 were canceled and claims 43-58 were added. Claims 43-58 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following objections are being maintained:

The attempt to **incorporate essential materials** into this application on page 4 by reference to patent applications which have not been allowed is improper because essential materials can only be incorporated by reference to (1) a U.S. patent or (2) an allowed U.S. application meeting the conditions set forth in MPEP 608.01(p) section B. See In re Fouche 169 USPQ 429:439 F.2d 1237 (CCPA 1971).

New Grounds of Rejection

Claim Rejections 35 USC 112

5. Claims 43-50 and 52-57 are rejected under 35 USC 112, first paragraph essentially for the reasons previously set forth in Section 11 of Paper No. 6 on pages 6-7 and in Paper No.16, Section 7, page 3 drawn to the rejection of claims 20, 22, 24-30, 32-34 and 36-42.

Arguments drawn to the rejection of the canceled claims are relevant to the instant rejection.

Applicant argues that (a) the ordinarily skilled artisan would have been able to use the general knowledge in the art and available techniques to make and use the claimed invention and cites DeGeorge v. Bernier "An invention need not explain every detail since he is speaking to those skilled in the art", (b) if testing is merely routine or if the specification gives a reasonable amount of guidance with respect to the direction in which the experimentation should proceed, then experimentation is not undue. Details of the sequence of the HSV-1 virus have been provided and other mutants of HSV have been described, i.e. R3616 and molecular techniques with which to produce mutants within the scope of the present claims are common general knowledge. The arguments have been considered but have not been found persuasive because (a) and (b) a review of DeGeorge v. Bernier reveals that the case is drawn to an apparatus drawn to the operation of a data processing system printer which is an art that is not analogous to the claimed method of treating cancer with an undefined mutated virus, wherein the fact pattern is not the same and therefore the findings in said case cannot be extrapolated to the enablement of the instant invention. Further, the mutations as claimed are unlimited and can be made in any portion of the HSV-1. As previously disclosed, the effects of these mutations on virus function are not predictable. Although the specification provides guidance on the sequence of the HSV-1 virus and molecular techniques with which to produce the mutants and points to a specific mutant R3616, this information is not sufficient to enable the claims because applicant has not taught where and how the sequence of HSV-1 virus is to be mutated for the virus to function as claimed and the R3616 mutant does not provide enough information to enable the broadly

worded claims. Other than providing a description of very specific mutations within gamma 34.5 in the long repeat region of HSV-1, the instant specification does not disclose a general principal upon which the instant invention is based and the mutations presented in the instant application to enable the scope of the invention cannot be extrapolated to the broadly claimed mutant herpes simplex virus-1 claimed. One skilled in the art is limited to essentially random production of mutants. The amount of experimentation necessary to screen the vast number of mutants encompassed by the claims requires undue experimentation. In view of the above and for the reasons previously set forth, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

6. Claims 43-50 and 52-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a metastatic tumor which occurs in but does not originate from the CNS comprising intra tumoral or intracranial injection of HSV-1 wherein the HSV-1 has a non-functional gamma 34.5 gene in the long repeat region, wherein HSV-1 infects the tumor cells of the tumor, does not reasonably provide enablement for a method of treating a metastatic tumor or melanoma comprising administering mutant HSV, wherein the HSV-1 has a non-functional gamma 34.5 gene in the long repeat region or a method of treating melanoma in a human comprising administering mutant HSV, wherein the HSV-1 has a non-functional gamma 34.5 gene in the long repeat region. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to administering a mutant HSV for the treatment of a metastatic cancer, melanoma. This includes any type of administration, including intra tumoral, intracranial or systemic. The specification teaches that the HSV mutant can be administered by injection directly into the tumor or into the blood stream feeding the tumor (p. 8) and exemplifies the intra tumoral injection of the mutant 1716 (p. 20) and the intracranial injection of mutant 1716 (p. 28). One cannot extrapolate the teaching of the specification to the scope of the claims because there is no teaching of how to deliver the mutant HSV-1, as claimed, to the site of action other than that cited above. It is clear that an anti-tumor agent must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear that, as taught by US Patent No. 5,585,096, that HSV has a very broad host range and seems capable of infecting all cell types in the CNS. Thus it would be expected that the mutant virus would be taken up by a broad variety of cells. Exacerbating the problem is the fact that the virus may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, and clearly would be expected to be absorbed by cells and tissues where it does not have the desired effect, and finally circulation into the target area may be insufficient so that a large enough local concentration may not be established. In addition, US Patent No. 5,585,096 specifically teaches that because of the broad host range, the virus needs to be targeted to tumor in order to achieve tumor-specificity (col 10, lines 40-50). The specification provides insufficient

guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. The specification is objected to and claims 51 and 58 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to mutant virus strain 1716.

It is unclear if mutant virus strain 1716 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to mutant virus strain 1716, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above virus, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed virus is an unpredictable event.

Applicant has not disclosed the deposit of mutant virus strain 1716. If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of

record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Claim Rejections 35 USC 103

8. Claims 43-58 are rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,585,096 in view of Olofsson et al (Arch. Virol., 1993, 128:241-256), Davey et al (Neurosurgery, 1991, 28:8-14), WO 92/13943 (IDS item) and Market et al, (Neurosurgery, 1993, 32:597-603, IDS item).

The claims are drawn to a method of treating a metastatic tumor which occurs in but does not originate from the CNS of a human, which method comprises the step of administering an effective amount of HSV-1 which has a non functional gamma 34.5 long repeat region, wherein the tumor occurs in brain, wherein it is metastasized melanoma, wherein the virus is a mutant strain 17 virus, wherein it has been modified by deletion within the BAMH1 s restriction fragment, wherein the deletion is from 0.1 to 3 kb, from 0.7 to 2.5 kb, wherein it is a 759 bp deletion in the gamma 34.5 gene, wherein it is strain 1716.

US Patent No. 5,585,096 teaches a method of treating cancer in a human comprising administering an HSV-1 deletion mutant with a 1000 bp deletion in the gamma 34.5 gene which results in a non-functioning gamma 34.5 long repeat region, wherein the mutant is replication competent in dividing but not nondividing cells but

is not neurovirulent (col 1) wherein the cancers treated include central nervous system tumors in brain, such as glioblastoma and include melanoma (see col 3) and teaches administration of the construct by direct intra neoplastic inoculation (p. 12). The reference teaches as set forth above but does not teach a method wherein the tumor treated is a metastatic melanoma in brain or a method wherein the deletion mutant is strain 1716.

Davey et al teach that melanoma metastasizes to the brain and that such metastases are often treated with whole-brain irradiation, but with limited benefit (see abstract).

Olofsson et al teach that HSV-1 infects metastatic melanoma cells (see p. 250).

WO 92/13943 teaches HSV-1 mutant 1716 (see claim 7) and teach that 1716 is a deletion mutant wherein there is a 759 bp deletion (p. 4) in the gamma 34.5 gene which is found within the BamH1 s restriction fragment of the RL terminal repeat (p. 3) wherein the mutant lacks neurovirulence (p. 1).

Market et al teach a mutant HSV-1 called R3616 with decreased neurovirulence when compared to HSV-1 (p.598, col 2), containing a 1000 bp deletion in gamma 34.5 which, when tested in an intracranial glioma model significantly prolonged average survival without producing premature encephalitic deaths (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the 1716 of WO 92/13943 for

the construct of US Patent No. 5,585,096 in the method of US Patent No. 5,585,096 and one of ordinary skill in the art would have expected to successfully substitute the 1716 of WO 92/13943 for the construct of US Patent No. 5,585,096 in the method of US Patent No. 5,585,096 because both constructs have decreased neurovirulence associated with the deletion of gamma 34.5 gene. Further, one of ordinary skill in the art would have expected to successfully substitute 1716 for the construct of WO 92/13943 because it was well known in the art that HSV-1 deletion mutants in the gamma 34.5 site were useful for treating cancer because Market et al teach that an HSV-1 deletion mutant containing a 1000 bp deletion in gamma 34.5, R3616 (which has also been shown to have decreased neurovirulence) is sufficient to treat tumor when administered in brain. Further, it would have been *prima facie* obvious to have used the method of US Patent No. 5,585,096 to treat metastatic melanoma in brain because US Patent No. 5,585,096 specifically teaches that the method is useful for treating tumors in brain and for treating melanoma and because Davey et al teach that melanoma metastasizes to the brain and because Olofsson et al teach that HSV-1 infects metastatic melanoma cells. One of ordinary skill in the art would have been motivated to treat metastatic melanoma with the method of of the combined references because Davey et al teach that cerebral metastases from malignant melanoma are often treated with whole-brain irradiation but with limited benefit and an additional form of treatment would broaden the attack on this malignancy.

9. All other objections and rejections recited in Paper No. 16 are withdrawn.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Ungar
Primary Patent Examiner
February 23, 2000